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DOI:

[10.1016/j.mri.2017.12.002](https://doi.org/10.1016/j.mri.2017.12.002)

Document Version

Peer reviewed version

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Citation for published version (APA):

Khosa, F., Clough, R., Wang, X., Madhuranthakam, A. J., & Greenman, R. L. (2017). The potential role of IDEAL MRI for identification of lipids and hemorrhage in carotid artery plaques. *Magnetic Resonance Imaging*.
<https://doi.org/10.1016/j.mri.2017.12.002>

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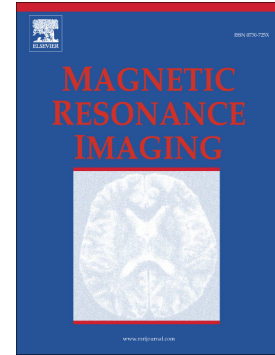
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PII: S0730-725X(17)30278-3
DOI: doi:[10.1016/j.mri.2017.12.002](https://doi.org/10.1016/j.mri.2017.12.002)
Reference: MRI 8879

To appear in:

Received date: 22 October 2017
Accepted date: 3 December 2017

Please cite this article as: Faisal Khosa, Rachel E. Clough, Xiaoen Wang, Ananth J. Madhuranthakam, Robert L. Greenman , The potential role of IDEAL MRI for identification of lipids and hemorrhage in carotid artery plaques. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Mri(2017), doi:[10.1016/j.mri.2017.12.002](https://doi.org/10.1016/j.mri.2017.12.002)

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The potential Role of IDEAL MRI for Identification of Lipids and Hemorrhage in Carotid Artery Plaques

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Word count: 2,727

Grant Support: This work was supported by the Center for Integrating Medicine and Innovative Technology (CIMIT) grant award number DAMD17-02-2-0006 supported with funding provided from U.S. Army Medical Research Acquisition Activity (USAMRAA). Dr. Khosa is the American Roentgen Ray Society Scholar (2013-2016) and Canadian Radiological Foundation Leadership Scholar (2017).

Key words: Vessel wall imaging, Water fat imaging, Spectroscopic imaging, MR angiography (MRA), Spectroscopic quantitation

Abbreviations:

IDEAL : Iterative decomposition of water and fat with echo asymmetry and least squares estimation

SIR: Signal intensity ratio

CNR: Contrast to noise ratio

MCW: Multiple contrast weighted

3D-TOF: 3D Time-of-Flight

T1W-BB-FSE: T1-weighted black blood fast spin echo

T2W-BB-FSE: T2-weighted black blood fast spin echo

ANOVA: Analysis of variance

MSDE: Motion-sensitization using a driven equilibrium

MPRAGE: magnetization prepared rapid acquisition gradient echo

Abstract

Hemorrhage and lipid deposits contribute to instability in atherosclerotic plaques. Unstable carotid artery plaques can lead to cerebral ischemic events. While MRI studies have shown the ability to identify plaque components, the identification of hemorrhage and lipids has proven to be problematic. The purpose of this study was to quantitatively evaluate the potential of the MRI fat/water separation method known as iterative decomposition of water and fat with echo asymmetry and least squares estimation (IDEAL) to complement and improve existing methods for the identification of hemorrhage and lipids in carotid artery plaques.

Fifteen asymptomatic subjects with 50-79% stenosis of at least one carotid artery were enrolled. Hemorrhage and lipid components within carotid plaques were identified using previously published criteria based on the multiple contrast-weighted (MCW) method (3D Time-of-Flight (3D-TOF), T1-Weighted (T1W) and T2-Weighted (T2W)). The hemorrhage:muscle, lipid:muscle and intra-plaque lipid:hemorrhage signal intensity ratios (SIR) and contrast to noise ratios (CNR) were measured on MCW and compared to IDEAL black-blood images.

No differences were found between any of the MCW methods for any of the SIRs measured. The IDEAL Fat images had higher lipid:muscle and lipid/hemorrhage SIRs ($p < 0.001$) compared to IDEAL water and all MCW image sequence types. The mean values of IDEAL Fat hemorrhage:muscle SIR and CNR were nearly unity (1.1 ± 0.6) and nearly zero (0.1 ± 1.1), respectively. The IDEAL Water imaging was not significantly different than any of the MCW methods for any of the SIRs or for the hemorrhage:muscle CNR of 3D-TOF, while its CNRs

were significantly higher than IDEAL Fat lipid:muscle ($p < 0.05$) and lipid:hemorrhage ($p < 0.001$) and all MCW methods ($p < 0.001$).

The addition of IDEAL water and fat imaging to the MCW method shows potential to improve the identification of hemorrhage and lipid structures in carotid artery plaques.

1. Introduction

Atherosclerosis is a chronic inflammatory process responsible for a host of disease processes including, but not limited to coronary events, stroke, peripheral vascular disease and hypertension [1,2]. Most acute cerebral ischemic events such as stroke are caused by rupture of unstable plaques in the carotid artery [3]. Hemorrhage and large necrotic lipid cores are morphological features of arterial plaques that play a key role in plaque rupture [1,4,5]. Hemorrhage contributes to enlargement of the core by promoting the deposition of free cholesterol and infiltration of macrophages and its presence may be an indication that a plaque is progressing toward an unstable state [4,5]. Previous studies have demonstrated that a necrotic lipid core with a thin fibrous cap presents a significant increased risk for plaque rupture, resulting in a thromboembolism [6-10], the cause of most strokes [1].

Over the past decade, the potential of magnetic resonance imaging (MRI) to characterize arterial plaques has been studied [6,11-13]. The soft tissue contrast capabilities without the need for iodinated contrast and the non-ionizing nature of MRI makes it highly suited for the in vivo study of arterial plaques, especially for longitudinal studies. Currently, the most widely accepted MRI method for plaque evaluation is based on the acquisition of images from multiple scans with different contrast weightings. This multiple contrast-weighted (MCW) [11-15] approach relies on inherent differences in tissue proton relaxation properties to identify individual plaque components and has been validated by comparing in vivo MCW imaging findings to histology in plaques that have been subsequently excised [16-19]. The MCW method for the identification of a plaque feature, such as hemorrhage or a lipid region involves comparing the signal intensity of

the feature to that of adjacent muscle tissue in images with different acquisition weightings [6,20]. However, signal intensity differences among plaque components and their ratios with muscle tissue can be subtle making identification challenging. In particular, the delineation of lipid content and hemorrhage has been problematic [6,13].

We hypothesized that acquiring separate lipid and water images using chemically selective MRI methods may improve the conspicuity of lipids and hemorrhage in atherosclerotic plaques and compliment the information that results from analysis of images acquired using MCW imaging. The chemical-shift-based water-fat separation MRI technique known as iterative decomposition of water and fat with echo asymmetry and least squares estimation (IDEAL) [21] has been validated [22,23] and is widely accepted as an accurate and robust method for fat-water separation. It has been used in the abdomen [21,24,25], head and neck [24], pelvis [24,26], for musculoskeletal imaging [21,23-26] and to evaluate fatty infiltration of the liver [22,27] with optimal SNR and immunity from magnetic field inhomogeneities.

The purpose of this work was to measure and evaluate image performance parameters in IDEAL Fat and Water images of carotid artery plaques and compare the results to those from images acquired at corresponding locations using conventional MCW imaging methods.

2. Materials and Methods

This HIPAA-compliant study was approved by our institution's Committee on Clinical Investigations. All subjects provided written informed consent for their participation in the study. Fifteen patients with asymptomatic carotid artery disease and 50-79% stenosis of at least one carotid artery as determined by ultrasound examination were enrolled. All patients underwent MRI examination on a 3.0 T whole body system (GE Medical Systems, Waukesha, WI). All subjects provided written informed consent for their participation in the study.

2.2 MRI Imaging Protocol:

The patients were positioned supine on the scanning table. A custom designed four-coil bilateral carotid artery array (Nova Medical, Wilmington, MA) was placed on the patients' necks. The array consisted of 2 overlapping coils placed on each side of the neck. Localizer scans were performed and the carotid bifurcation was identified.

The MRI protocol consisted of 3 scans for the MCW assessment: 3D time-of-flight (3D-TOF); 2D T1-weighted black blood fast spin echo (T1W-BB-FSE); and 2D T2-weighted black blood fast spin echo (T2W-BB-FSE) imaging. Fat/water IDEAL imaging was performed using a 2D T1W-BB-FSE pulse sequence [21]. The following acquisition parameters were common to all of the scans (MCW and IDEAL): axial orientation, 16 slices, slice gap = 0, field-of-view (FOV) = 16 x 12 cm, acquisition matrix = 256 x 192, slice thickness = 2 mm, receiver bandwidth = ± 16 kHz. The TR/TE for the MCW 3D-TOF, T1W-BB-FSE, T2W-BB-FSE acquisitions were 25ms/2.3ms, 800ms/11ms, and 2000ms/66ms, respectively. The TR/TE of the IDEAL T1W-BB-

FSE acquisition was 800ms/11ms. The time required for the MCW scanning was: 3D-TOF: 5 minutes 12 seconds; T1W-BB-FSE: 5 minutes, 7 seconds; and T2W-BB-FSE: 12 minutes, 48 seconds. The time required for completing the single-scan IDEAL T1W-BB-FSE water and fat imaging was 15 minutes and 22 seconds. All MCW and IDEAL imaging covered the same range and the slice locations corresponded between all scans.

2.3 MRI image review and measurement criteria:

Identification of hemorrhage and lipids was performed by two independent reviewers using the conventional MCW images. The assessment was carried out using published criteria developed and validated for MCW studies [6,13,16] as described in Table 1. The reviewers then compared their results and came to a consensus decision for any differences in the identity of the plaque constituents that were found between their independent reviews.

Signal intensities were measured by placing regions of interest (ROIs) on features (hemorrhage or lipid) within plaques and in nearby muscle tissue on a PACS workstation DICOM viewer (OsiriX v. 5.7.1, Los Angeles, CA). Determination of the type of tissue being evaluated was based on the ratio of the of signal intensity in plaque constituents with that of adjacent muscle tissue that was approximately the same distance from the surface coil as the lesion being examined [6,13,16,28,29]. After the plaque features were identified using the MCW method the ROI measurements were repeated in the corresponding locations on the Water and Fat T1W IDEAL images.

When all ROI measurements were complete on all of the MCW and IDEAL images, three signal intensity ratios (SIRs) were calculated to compare the relative signal intensities of hemorrhage and lipid regions to the reference muscle tissues between the different image acquisition types. The three ratios were: 1) hemorrhage:muscle; 2) lipid:muscle; and 3) lipid:hemorrhage when hemorrhage and lipid tissue were found in the same lesion. The hemorrhage:muscle, lipid:muscle and lipid:hemorrhage contrast to noise ratio (CNR) was also calculated using noise signal intensity values measured in the background (air) regions of the images. IDEAL imaging requires a longer scanning time than corresponding conventional techniques, resulting in a square root of 3 improvement in signal to noise ratio (SNR) [21]. When calculating CNR, the signal to noise ratios of the tissues measured in the IDEAL images were corrected to account for the square root of 3 difference in SNR.

2.4 Statistical analysis:

A one-way ANOVA analysis was used to compare the SIR and CNR results of the IDEAL Fat and Water imaging and the conventional MCW imaging methods. The statistical analysis was performed using GraphPad Prism software (version 4.0c, GraphPad Software, San Diego, CA USA, www.graphpad.com).

3. Results

A total of 240 image locations were acquired from all 15 patient exams. Using the criteria in Table 1, hemorrhage was identified at 54 image locations and lipids at 26 locations. Hemorrhage and lipid tissue were both identified within the same lesion at 24 image locations.

Figure 1 shows conventional MCW 3D-TOF (a), T1W-BB-FSE (b), T2W-BB-FSE (c) and IDEAL T1W-BB-FSE Water (d) and Fat (e) images of an axial view of the right internal carotid artery of one of the study subjects. A large lesion is seen adjacent to the lumen of the artery (arrow). According to the criteria listed in Table 1, the combined findings of hyper-intense signal compared with adjacent muscle in the 3D-TOF and T1W-BB-FSE images and iso-intense signal in the T2W-BB-FSE image, the lesion is identified as hemorrhage. The signal in the lesion is hyper-intense in the IDEAL Water image (d) and iso-intense with adjacent muscle in the IDEAL Fat (e) image (the hemorrhage and muscle signal intensities are both at the level of the noise in the Fat image).

A lesion with variable signal intensity is seen in Figure 2 surrounding much of the lumen. In the MCW 3D-TOF image (a), there are multiple small regions of iso-intense signal distributed throughout the lesion (arrows). The corresponding regions are hyper-intense in the T1W-BB-FSE image (b) and again iso-intense in the T2W-BB-FSE image (c). Based on the criteria in Table 1, these multiple small regions were identified as containing lipids. The same regions are hypo-intense in the IDEAL Water (d) image and hyper-intense in the IDEAL Fat (e) image.

The mean values of the hemorrhage:muscle, lipid:muscle and the lipid:hemorrhage SIRs for each imaging method are listed in Table 2 and shown graphically in Figure 3. There were no significant differences in the hemorrhage:muscle SIR values between IDEAL Water and IDEAL Fat (Fig 3a). Nor were there any differences between IDEAL Water and any of the MCW imaging methods. IDEAL Water and T1W imaging had similar values. The 3D-TOF hemorrhage:muscle SIR was significantly larger than that of the IDEAL Fat images ($p < 0.01$) with no difference between the IDEAL Fat images and the T1W, T2W and IDEAL Water images.

There was no difference in the lipid:muscle SIR among the IDEAL Water imaging and any of the MCW imaging methods (Fig 3b). The IDEAL Fat imaging SIR was, however significantly greater than the SIR of any of the MCW methods and the IDEAL Water imaging ($p < 0.001$ for all).

There again was no difference between the IDEAL Water imaging and any of the MCW imaging methods for the lipid:hemorrhage SIR (Fig.3c). The IDEAL Fat imaging SIR was again significantly greater than all other imaging methods ($p < 0.001$ for all).

No statistical differences were found among any of the MCW imaging methods for hemorrhage:muscle, lipid:muscle or lipid:hemorrhage SIR.

The results of the CNR calculations are listed in Table 3 with the corresponding graphical representations in Figure 4. While the IDEAL Water hemorrhage:muscle imaging CNR values were larger than those of the 3D-TOF imaging, they were not significantly different. The hemorrhage:muscle CNR of the IDEAL Fat imaging was nearly zero and was not significantly different than that of the T2W imaging but significantly lower than the IDEAL Water, 3D-TOF and T1W imaging ($p < 0.001$ for all). The 3D-TOF CNR was significantly larger than that of the T2W imaging ($p < 0.01$) but not different from the T1W imaging.

The lipid:muscle CNR of IDEAL water imaging was significantly larger than IDEAL Fat and all of the MCW imaging methods ($p < 0.001$ for all). The IDEAL Fat imaging lipid:muscle CNR was significantly greater than all of the MCW methods ($p < 0.05$ for T1W and $p < 0.01$ for all others).

No differences were found for the lipid:hemorrhage CNR between the IDEAL Fat imaging method and any of the MCW imaging methods (Fig 4c). The magnitude of the IDEAL Water lipid:hemorrhage CNR was significantly greater than all other imaging methods ($p < 0.001$ for all). It is noted that the lipid signal intensities were lower than the hemorrhage signal intensities for the IDEAL Water, 3D-TOF, T1W and T2W imaging but the lipid signal intensity values of the IDEAL Fat images were higher than those of the hemorrhage.

As stated above, there was no difference between the hemorrhage:muscle CNR of the 3D-TOF imaging and the T1W imaging and no difference between the T1W and T2W imaging methods.

No differences were found among any of the MCW imaging methods for the lipid:muscle or the lipid:hemorrhage CNR values.

4. Discussion

Most of the mean SIR values found in this study for hemorrhage:muscle and lipid:muscle of 3D-TOF, T1W and T2W imaging agree closely with the criteria in Table 1, although the mean value of the T2W hemorrhage:muscle SIRs that were measured here reflected hyper-intensity, which conflicts with the criterion of hypo- to Iso-intensity for identification of hemorrhage and lipids (Table 2).

The MCW method for identifying lipids and hemorrhage in carotid artery plaques relies on a specific combination of SIR values measured as being hypo-, iso- or hyper-intense compared to adjacent muscle tissue for each of the three different imaging methods. In this study, the measured MCW SIR values were not statistically different from each other. This may introduce ambiguity, which could result in errors when using the MCW method with the imaging types that are currently used. Further, within the range of a single standard deviation, any of the MCW imaging methods could give SIR values, that are hypo-, iso- or hyper-intense for both hemorrhage:muscle and lipid:muscle ratios (Table 2).

The similarity between the hemorrhage:muscle SIR values for IDEAL Water and T1W imaging would be expected since hemorrhage and muscle are both mostly water and both imaging methods are based on the T1W FSE method. Further, the IDEAL Water imaging was not found to be different than the T1W imaging in any of the three SIR comparisons. However, the significantly higher hemorrhage:muscle and lipid:muscle CNR of IDEAL Water imaging compared to that of the T1W imaging may improve the conspicuity of both hemorrhage and

lipids during the evaluation process. Also, the significantly higher lipid:hemorrhage CNR of the IDEAL Water imaging may be an aid in differentiating regions of lipid and hemorrhage. It is noted that IDEAL Water lipid signal was hypo-intense compared to both the muscle or hemorrhage signals. Further studies may determine whether substituting IDEAL T1-BB-FSE Water imaging for T1-BB-FSE imaging in the MCW method may improve the identification of lipids and hemorrhage.

The mean IDEAL Fat hemorrhage:muscle SIR value was nearly equal to unity since the image intensities of both hemorrhage and muscle are at the level of the background noise. Similarly, the mean hemorrhage:muscle CNR is nearly zero because the hemorrhage and muscle are both at the level of the background noise. These might be useful criteria for identifying hemorrhage. For example, if a lesion has a hyper-intense SIR on an IDEAL Water imaging or meets the existing criterion for hemorrhage on one or more of the current MCW imaging methods, an iso-intense SIR and near zero CNR on a corresponding IDEAL Fat image might increase the confidence that the lesion is hemorrhage.

The significantly higher mean SIR values for the IDEAL Fat lipid:muscle and lipid:hemorrhage ratios may make it a definitive marker for identification of plaque lipids and differentiator between plaque lipids and hemorrhage.

This is a retrospective observational study from single institution and is limited by its small sample size. Further validation of IDEAL as a technique for the assessment of atherosclerotic plaques should involve a larger study population and histological confirmation of excised

plaques. Multicenter trials would further validate these results. Our study population comprised of asymptomatic individuals so the results are not generalizable. We also do not have follow-up on outcome related to plaque composition to determine which particular plaque subtypes may be more predictive of events.

An additional limitation of this study is that the IDEAL method used here creates a fat (triglycerides) image from the methylene spectral peak. An abundance of cholesteryl ester (CE) is associated with instability in atherosclerotic plaques and it makes up the largest fraction of the lipid core [10]. This may be the reason that the lipid:muscle and lipid:hemorrhage CNR values in the IDEAL Fat images were low in this study. Cholesteryl ester is identified by the methyl peak of the lipid spectrum and is located 0.4 ppm from the methylene peak. Although the IDEAL Fat images in this study were acquired from the methylene peak, the results demonstrate the feasibility of identifying lipids within carotid plaques. A modified version the IDEAL method has been used to separate individual carbon-13 metabolites [30]. With appropriate manipulation of echoes and echo timing, images can be created that are based on the methyl peak, thereby identifying the CE component of the lipid pool.

While this study did not compare in vivo imaging results to excised plaque histology directly, the MCW method used here to initially identify plaque components has been validated using excised specimens [16-19].

The acquisition time of the T1W IDEAL imaging was substantially longer than that of any of the MCW imaging methods. Our implementation of IDEAL used a multi-acquisition approach, where each of the echoes required for IDEAL processing are acquired in separate repetitions. Future implementations with a multi-echo approach [31] to acquire all echoes required for IDEAL processing in the same repetition could reduce the scan time. Additionally, it has been recently demonstrated that motion-sensitization using a driven equilibrium preparative (MSDE) sequence can provide improved suppression of luminal blood in the presence of complicated flow patterns at the carotid artery bifurcation [31]. The MSDE method can also be used to improve scanning efficiency by allowing the acquisition of 3D volumes, which can provide thinner slice thicknesses [25, 32, 33] and acquisition of multiple slices with a single preparation sequence. The implementation of IDEAL in MSDE sequences could provide improvements in plaque component identification with higher scanning efficiency.

While some studies have shown that the magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence can be used to identify intraplaque hemorrhage [34, 35] it can be difficult to find optimal inversion times due to variability in blood flow [35]. Additionally, it may not be reliable in differentiating hemorrhage from lipids since both plaque constituents have short T1 relaxation times.

The results of this study suggest that MCW imaging may be improved with the addition of T1-weighted BB-FSE IDEAL Water and Fat imaging. The conspicuity of lipids and hemorrhage may improve, enhancing reader confidence as well as the sensitivity for detecting and identifying these plaque components. A higher CNR between hemorrhage and muscle and between lipids

and muscle afforded by IDEAL imaging may improve the accuracy of the existing MCW method. A higher CNR between lipid and hemorrhage suggests a higher conspicuity of the adjacent tissues, which may translate into improved sensitivity for detecting both lipid and hemorrhage tissues. It may also improve the ability to longitudinally follow the progress of medical therapies, as longitudinal studies have demonstrated that necrotic lipid core size may decrease with lipid lowering treatment [36] and the identification of patients with inadequate response to medical therapy that could benefit from more aggressive surgical or endovascular interventions to decrease their stroke risk.

Future studies comparing pre-surgical MCW and IDEAL imaging of carotid plaques with histological analysis of excised plaques may yield additional data that may help determine the role that IDEAL imaging could play in the identification of lipids and hemorrhage in vivo. A study using an IDEAL pulse sequence that is modified to identify CE rather than triglycerides may further determine the utility of IDEAL in the identification of lipids and plaque vulnerability.

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Tables

Table 1. Criteria for evaluating conventional Multiple Contrast Weighted (MCW) imaging

Feature	3D-TOF	T1W-BB	T2W-BB
Hemorrhage	Hyper	Iso/Hyper	Hypo/Iso
Lipid	Iso	Iso/Hyper	Hypo/Iso

Table 2. Mean values of the signal ratio (SIR) measurements for each image type.

	IDEAL Water (Mean \pm SD)	IDEAL Fat (Mean \pm SD)	3D-TOF (Mean \pm SD)	T1W-BB-FSE (Mean \pm SD)	T2W-BB-FSE (Mean \pm SD)
Hemorrhage/Muscle	1.3 \pm 0.3	1.1 \pm 0.6	1.4 \pm 0.5	1.3 \pm 0.2	1.2 \pm 0.4
Lipid/Muscle	0.8 \pm 0.3	3.3 \pm 1.5	1.0 \pm 0.2	1.1 \pm 0.3	1.1 \pm 0.4
Lipid/Hemorrhage	0.6 \pm 0.2	3.3 \pm 2.3	0.8 \pm 0.2	0.9 \pm 0.2	0.8 \pm 0.3

Table 3. Mean values of the contrast-to-noise ratio (CNR) measurements for each image type.

	IDEAL Water (Mean \pm SD)	IDEAL Fat (Mean \pm SD)	3D-TOF (Mean \pm SD)	T1W-BB-FSE (Mean \pm SD)	T2W-BB-FSE (Mean \pm SD)
Hemorrhage-Muscle	4.9 \pm 5.966	0.1 \pm 1.1	3.3 \pm 3.7	2.0 \pm 2.6	0.6 \pm 2.1
Lipid-Muscle	6.2 \pm 4.1	3.7 \pm 2.2	0.3 \pm 3.3	0.9 \pm 2.5	0.2 \pm 2.1
Lipid-Hemorrhage	15.0 \pm 9.0	3.4 \pm 2.4	4.2 \pm 2.9	1.8 \pm 2.1	1.8 \pm 2.7

Figure Legends

Figure 1. Multiple contrast weighted and IDEAL images of a large lesion (arrows) of uniform signal intensity adjacent to the left internal carotid artery (3D-TOF (a), T1W (b), T2W (c) IDEAL Water (d) and IDEAL Fat ((e)). Base on the criteria in Table 1, this lesion was identified as hemorrhage.

Figure 2. A semi-circular lesion adjacent to the right internal carotid artery with variable signal intensity in all MCW and IDEAL images. Multiple locations within the lesion met the criteria for the presence of lipid according to Table 1.

Figure 3. Bar graph plots of the results of the one-way ANOVA analysis of the SIR values.

Footnote: Bars with same symbols do not have statistical differences.

Figure 4. Bar graph plots of the results of the one-way ANOVA analysis of the CNR values.

Footnote: Bars with same symbols do not have statistical differences.

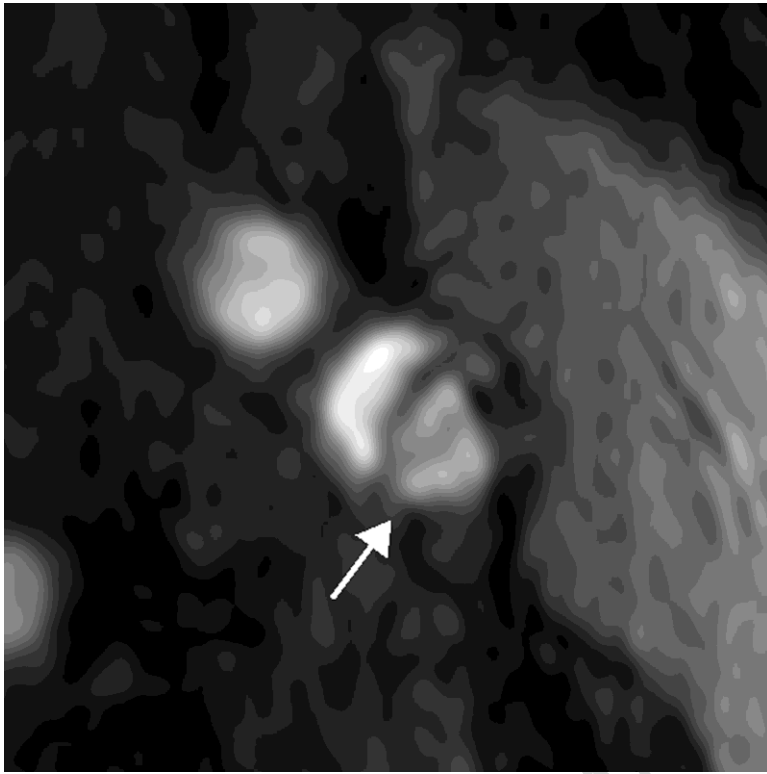


Figure 1a

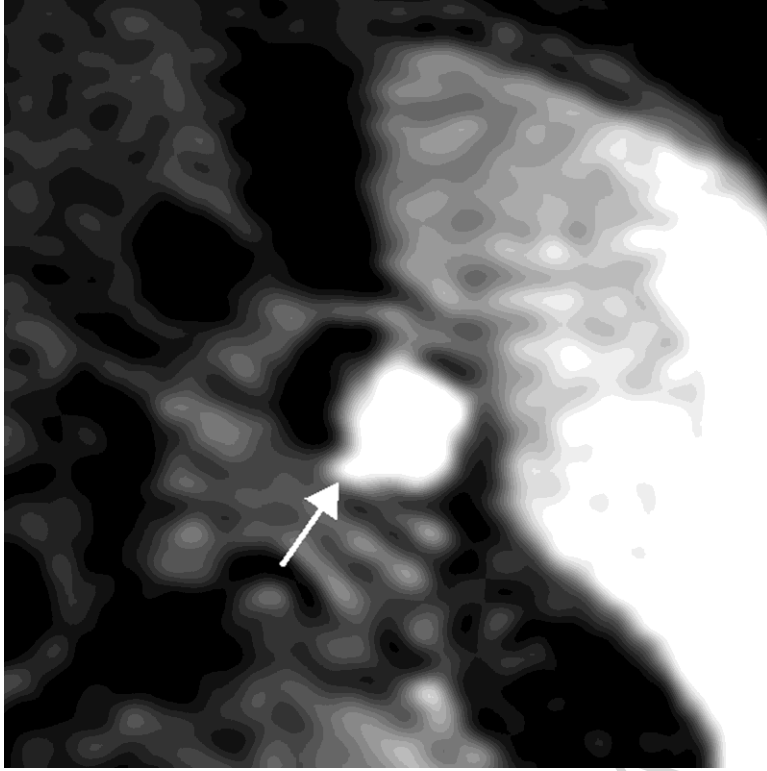


Figure 1b

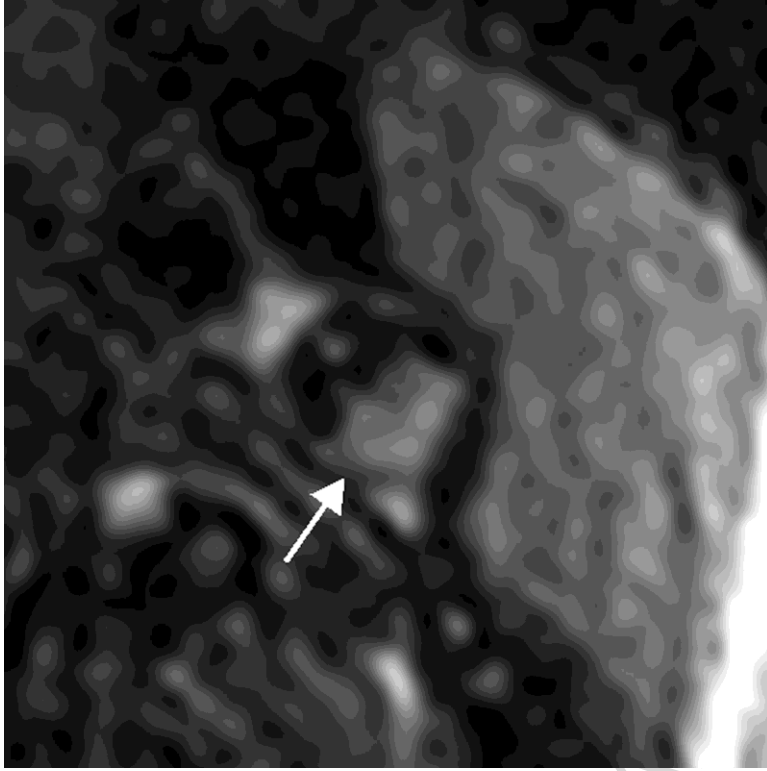


Figure 1c

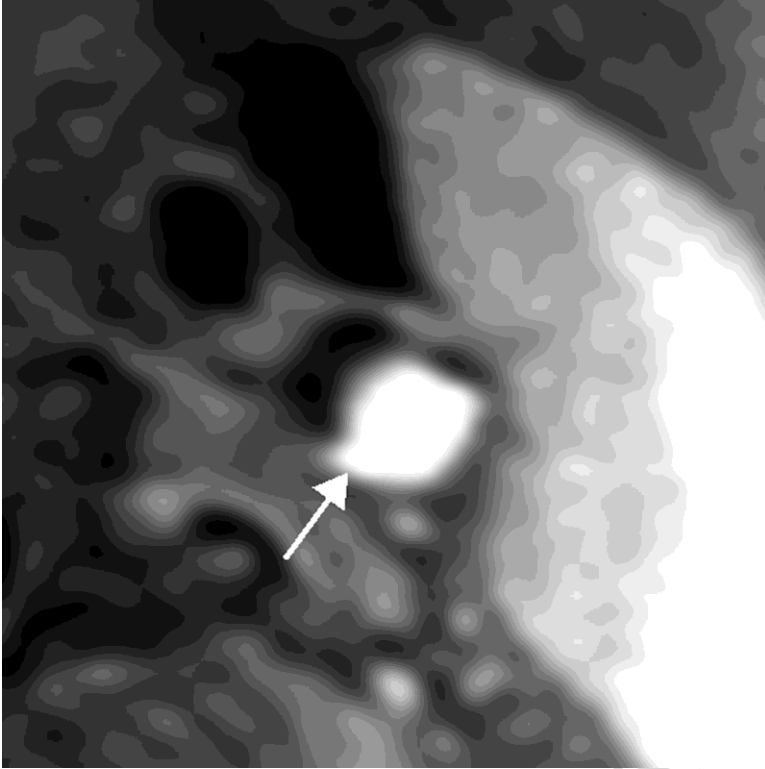


Figure 1d



Figure 1e

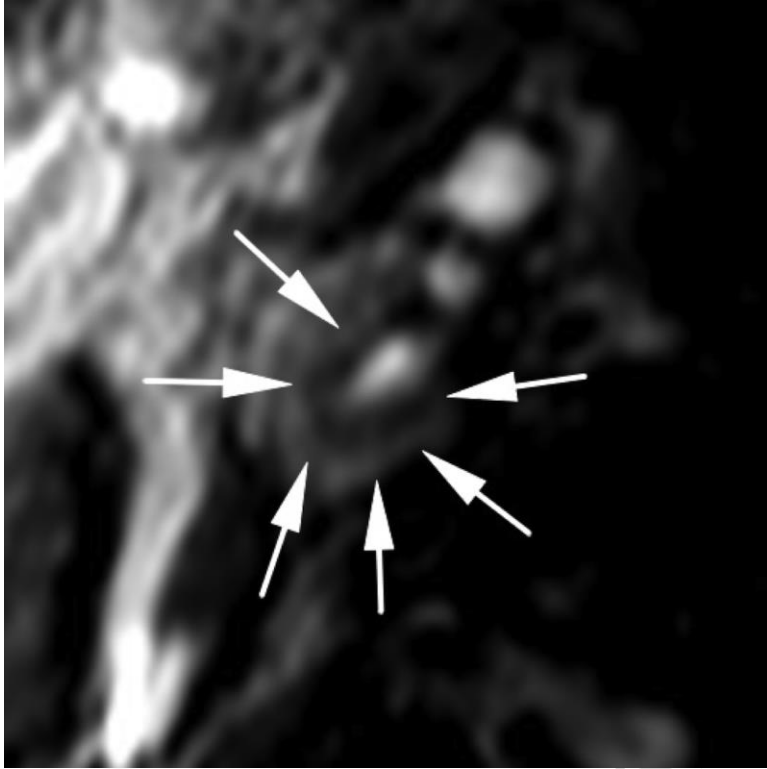


Figure 2a

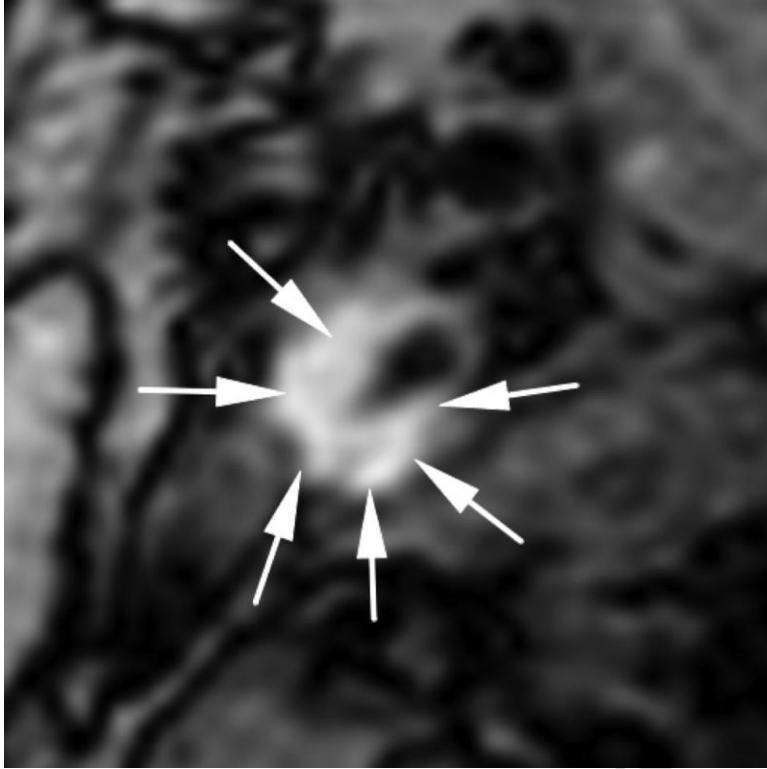


Figure 2b

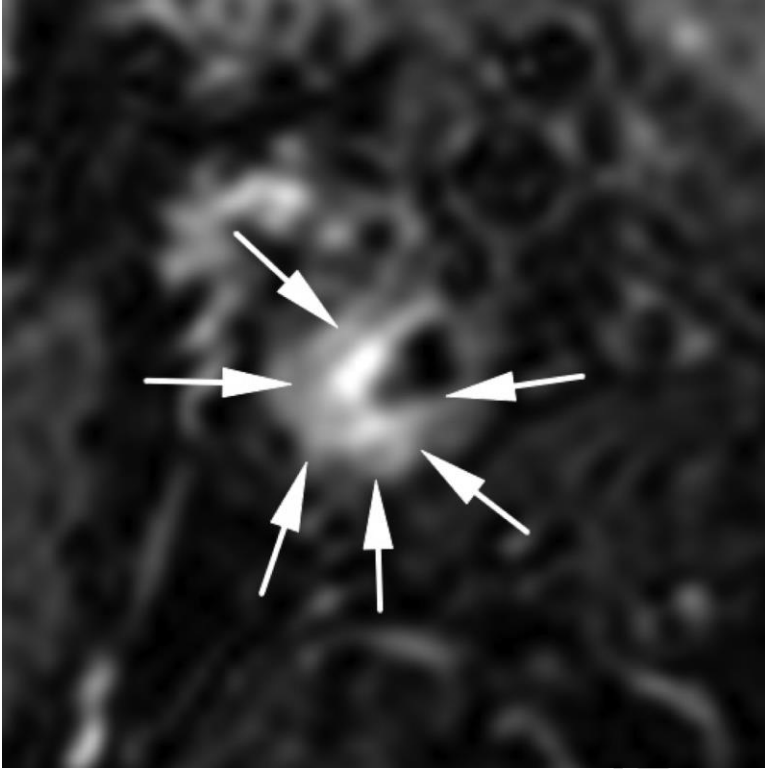


Figure 2c

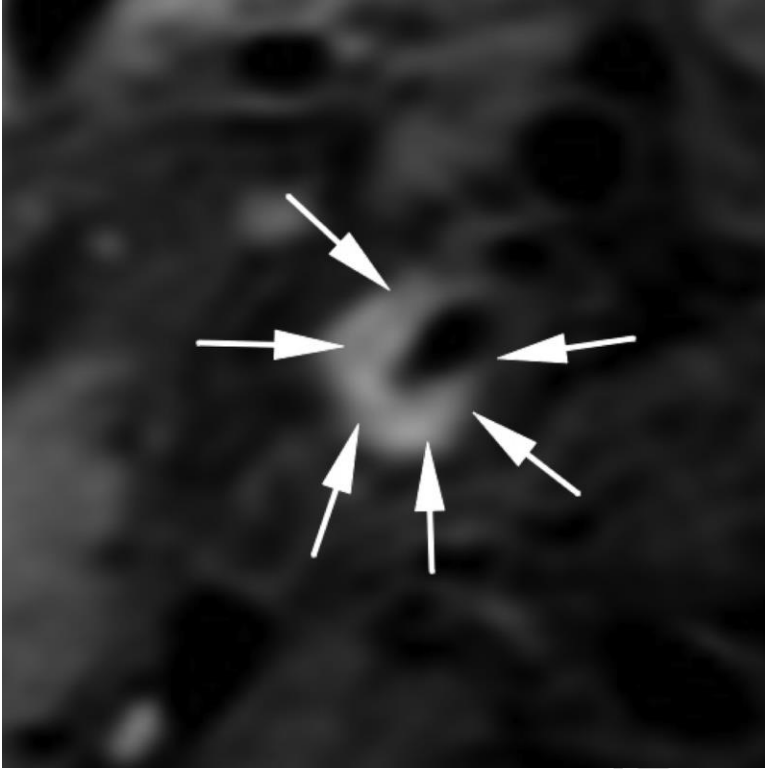


Figure 2d



Figure 2e

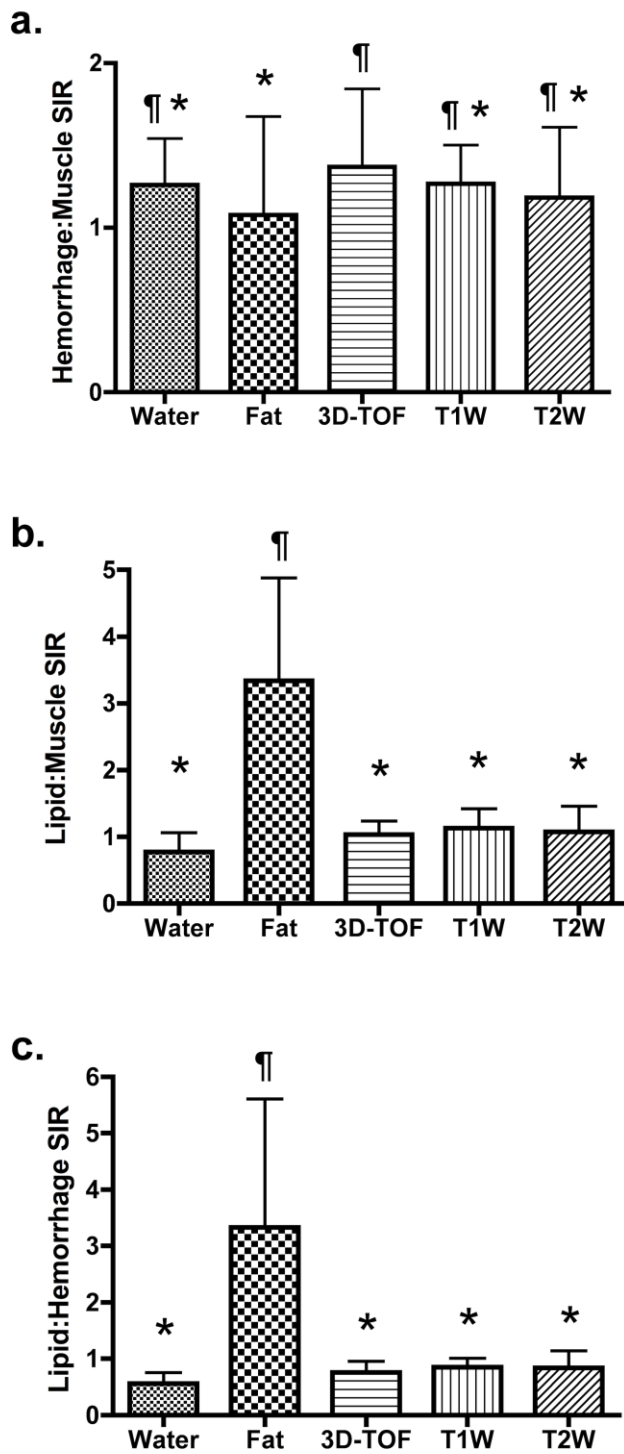


Figure 3

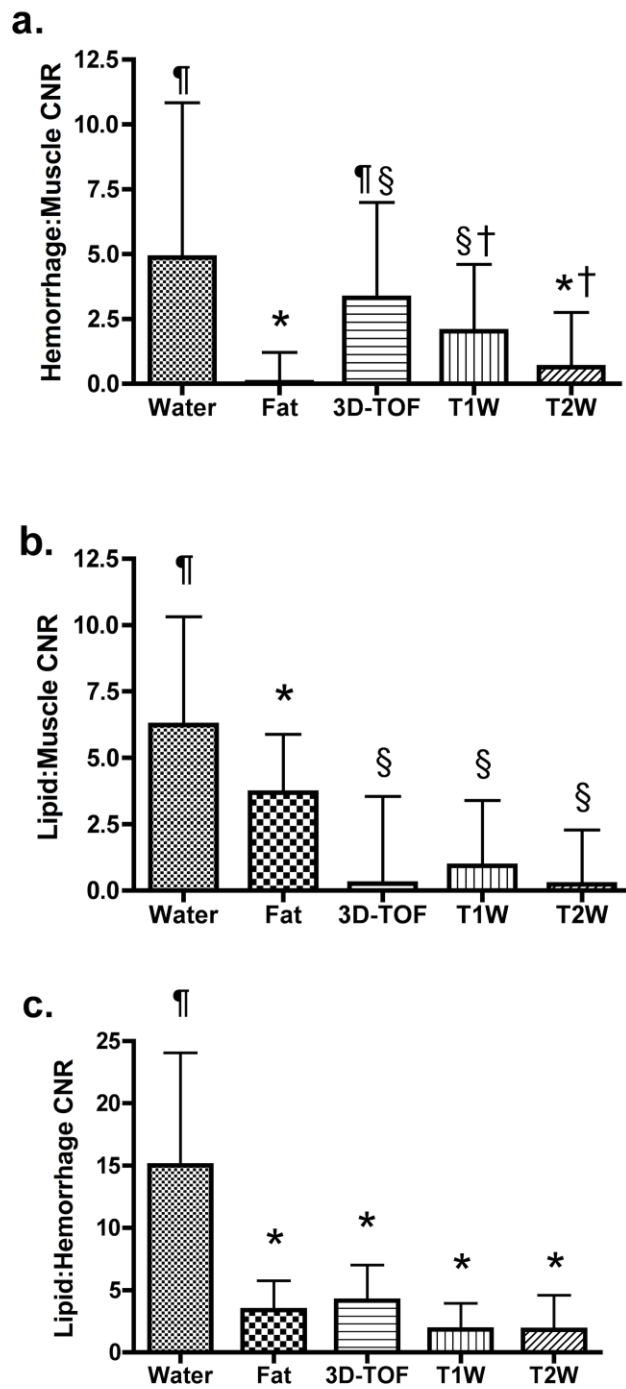


Figure 4

Highlights

- It was hypothesized that the iterative decomposition of water and fat with echo asymmetry and least squares estimation (IDEAL) MRI method may improve or compliment the multiple contrast weighted method for identifying unstable carotid artery plaques.
- The signal intensities of the muscle, intra-plaque hemorrhage, intra-plaque lipid and background noise were measured and the hemorrhage:muscle, lipid:muscle and intra-plaque lipid:hemorrhage signal intensity ratios (SIR) and contrast-to-noise ratios (CNR) were calculated.
- No differences were found in the SIRs between any of the multiple contrast weighted imaging methods.
- The fat and water images of the IDEAL MRI method showed improvement compared to some of the SIRs and CNRs that were measured.
- Combining IDEAL method water and fat imaging with the MCW method may improve the identification of unstable carotid artery plaques by MRI.